REMARKS

Claims 1-24 are pending in the application. Claims 1-19, 21, 23 and 24 have been amended. Support for the amendments can be found throughout the application and in the claims as originally filed. No new matter has been added. Any amendments to and/or cancellation of the claims should in no way be construed as acquiescence to any of the rejections and was done solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

In compliance with 37 C.F. R. §1.121, a marked up version entitled "Version with Markings to Show Changes Made," is attached hereto as Appendix I. In addition, for the Examiner's convenience, a clean copy of all the pending claims is set forth in Appendix II.

Oath/Declaration

The declaration was found defective on the ground that it has not been signed by co-inventor Jingde Zhu, in view of the letter Dr. Zhu filed on 9/15/2000 (Paper No. 13) with the PCT Legal Office expressing his desire to be involved with the prosecution of the application.

Accordingly, a new declaration in compliance with CFR § 1.67(a) and signed by Dr. Zhu is being filed concurrently herewith.

Claim Objections

Claim 1 was objected on the ground that the Preliminary Amendment filed on January 13, 1998, as containing changes not properly rewritten using appropriate bracketing. Applicants apologize for any misunderstanding. The wording of claim 1 in the Preliminary Amendment was the same as the originally filed claim, except for the deletion of the period between "controlled" and "by" on line 3 of the claim. This correction of the claim has been reiterated by the current amendment as requested by the Examiner.

Dependent claims 2-21, 23 and 24 were objected to for the use of the wording "A composition according to...". Accordingly, these claims have been amended to replace this phrase with "The composition according to...", as requested by the Examiner.

Claim 10 was objected to for the phrase "a said nucleic acid vector". Applicants respectfully submit that this language is in claim 11, not claim 10, and have amended claim 11 to correct this inadvertent typographical error as requested by the Examiner.

Claim Rejections under 35 U.S.C. §112, Second Paragraph

Claim 1 and its dependent claims were rejected as indefinite on the ground that

> [I]t is unclear whether there exists any promoter which meets the limitations of the claim or whether all promoters (except constitutive promoters) meet the recited claim limitations...because there is no context for knowing how to apply "suppressed" or "up-regulated" within the limited context of a "non-tumor cell"; use of the terms "suppressed' and "up-regulated" in relation to promoters is highly context specific and dependent on specific factors or stimuli which are not recited in the claim.

And, further

> [I]t recites a composition, which at a minimum, contains a first nucleic acid construct and a second nucleic acid construct; however, there is no clear structural nexus between these constructs and any of the genes or promoters recited...the

claims do not recite whether the genes or promoters are actually on the nucleic acid constructs, whether the promoters are operatively linked to the genes, or whether they merely represent the promoters that typically control expression of those particular genes in their native context.

Claim 1 has been amended to clarify the subject matter which Applicants view as the invention. Specifically, the presently claimed subject matter is directed to a composition comprising two nucleic acid constructs. The first nucleic acid construct comprises a first gene that is controlled by (*i.e.*, operatively linked to) a first promoter that is suppressed in non-tumor cells (*i.e.*, normal cells) relative to tumor cells. The second nucleic acid construct comprises a second gene whose gene product (e.g., antisense, ribozyme, transcriptional suppressor) suppresses expression of the first gene. This second gene is under the control (*i.e.*, operatively linked) to a promoter that is up-regulated in non-tumor cells (*i.e.*, normal cells) relative to tumor cells. As a result, there are two levels of control which suppress expression of the first gene in non-tumor cells: (1) regulation by a promoter whose function is suppressed in normal cells relative to tumor cells; and (2) further suppression by the gene product a second gene that is under control of a promoter that functions in non-tumor cells, but is suppressed in tumor cells.

Accordingly, Applicants respectfully submit that the language of claim 1 provides a clear structural and functional nexus between each of the recited elements (e.g., nucleic acid constructs, genes and promoters), and the skilled artisan would have no difficulty in determining whether a particular composition is within the metes and bounds of the claimed subject matter. Therefore, reconsideration and withdrawal of the rejection is respectfully requested.

Claims 2-4 were rejected as indefinite in the recitation of compositions defined by process steps in accordance with claim 1. This rejection has been obviated by the amendment of the claims as suggested by the Examiner.

Claims 6 and 7 were rejected as indefinite in the recitation of the term "suppression domain". This rejection has been obviated by the amendment of the claims as suggested by the Examiner.

Claim 9 and its dependent claims was rejected as lacking insufficient antecedent basis for the limitation "the same nucleic acid vector." This rejection has been obviated by the amendment of the claim as suggested by the Examiner.

Claim 12 was rejected as indefinite in the recitation of the term "CMB promoter," and claims 12 and 13 were further rejected as indefinite on the ground that the structural relationship between the second nucleic acid construct and the limitations recited in the claim is unclear. These rejections have been obviated by the amendment of the claim as suggested by the Examiner.

Claim 17 was rejected as indefinite on the ground that it is unclear how the term "antitumor agent" is defined. Applicants respectfully submit that the use of this term is consistent with its art-recognized meaning, e.g., an agent that counteracts, inhibits or suppresses tumor formation. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

Claims 20 and 21 were rejected as indefinite in the recitation of the phrase "[a] cell containing...," or "[a] cell according to...," on the ground that "it is not clear whether the claims are drawn to an isolated cell and/or whether they embrace a cell within e.g. a body." Applicants respectfully submit that the language of the claims is clear in that the

claims are not limited to isolated cells, but include all cells into which the first and second nucleic acid constructs of the invention have been introduced. Accordingly, Applicants respectfully request withdrawal of this rejection.

Claim Rejections under 35 U.S.C. §112, First Paragraph

Claims 1-13 and 20-24 were rejected for lack of adequate written description on the ground that the rejected claims embrace a broad range of promoters, while the specification:

> ...only discloses compositions comprising use of a first p53-responsive promoter down-regulated in non-tumour cells, but up-regulated in tumour cells carrying mutant p53, and further comprising a second wild-type p53-responsive promoter operatively linked to an effector product that down-regulates the first promoter in non-tumour cells,
>
> and further that,
>
> ...while the specification provides written description for various promoters responsive to wtp53, mutant p53, or to the absence of p53 (e.g., HSP70, MDR1, and PCNA), the specification fails to describe the other genuses of promoters up-regulated or down-regulated in tumour and/or non-tumor cells as recited in the claims with particularity to indicate that applicants had possession of the claimed invention.

Applicants respectfully traverse the foregoing rejection on the grounds that there is sufficient written description in Applicants' specification regarding the promoters that fall within the scope of the claims, to inform a skilled artisan that Applicants were in possession of the claimed invention at the time the application was filed, as required by section 112, first paragraph (see M.P.E.P. 2163.02).

"Written description may be satisfied through disclosure of relevant identifying characteristics, i.e., structure, other physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and

structure, or some combination of such characteristics." *Interim Guidelines for Examination of Patent Applications Under the 35 U.S.C. §112, First Paragraph Written Description Requirement.* Moreover, "[a] specification may, within the meaning of 35 U.S.C., § 112, First Paragraph, contain a written description of a broadly written claimed invention without describing all species that claim encompasses." *Utter v. Hiraga*, 845 F.2d 993, 6 USPQ2d 1709 (Fed. Cir. 1988).

Applicants respectfully submit that the claimed genus of promoters of the present invention is adequately defined by structural features that are described in the specification, recited in the claims, and commonly possessed by its members. To begin with, the specification teaches that the promoters possess certain functional characteristics, *i.e.,* promoters that are suppressed in non-tumor cells relative to tumor cells for the first nucleic construct, and promoters that are up-regulated in non-tumor cells relative to tumor cells for the second nucleic acid construct. The specification also provides working examples including the wtp53 and mutant p53 promoters, and discloses examples of other promoters that are expected to work in the invention as claimed (e.g., at page 12). Further, the specification provides guidance which would allow the skilled artisan to test any promoter to determine whether it has the required characteristics (e.g., at pages 14-15, and in the assays disclosed in the examples at pages 28-45).

In summary, Applicants have described a genus of promoters based on functional features, have provided examples of members of this genus, as well as guidance to determine whether any other promoter has the required functional characteristics. Such guidance clearly constitutes more that a mere statement regarding promoters that are part of the invention and mere potential methods for isolating them. Therefore, detailed

chemical structures for each and every promoter that is within the scope of the claims is not required. Accordingly, Applicants request reconsideration and withdrawal of this rejection.

Claims 1-24 were rejected on the ground that the specification "fails in its burden to provide sufficient guidance on how to identify other genes or promoters [other than p53] commensurate with the scope [of] the claimed invention." Applicants respectfully traverse this rejection.

It is well established that in order to meet the statutory requirements of 35 U.S.C., first paragraph, "[n]othing more than objective enablement is required, and therefore it is irrelevant whether this ***teaching is provided through broad terminology*** or illustrative examples." *In re Wright*, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993). Further, enablement is not precluded by the necessity for some experimentation (see, *e.g.*, *In re Wands* 8 USPQ2d 1400-1407, 1404 (CAFC, 1988)).

As discussed previously, the specification provides both working examples and ample guidance for testing any promoter or gene to determine whether it functions within the scope of the claimed invention. Specifically, a number of assays are provided to test whether a promoter or gene functions in either non-tumor or tumor cells. For example, transcriptional assays are provided at pages 28-33, assays to test various gene products for the ability to suppress expression of genes within the first nucleic acid construct are disclosed at pages 33-38, assays to test the ability of the first gene to function in tumor cells are disclosed at pages 39-45, and assays to test the constructs of the invention for activity *in vitro* and *in vivo* are disclosed at pages 58-59.

In view of the guidance provided, the skilled artisan would view any experimentation that may be required to make or use promoters or genes within the scope of the present claims as routine, not undue, experimentation. Thus, Applicants respectfully submit that the teachings of the specification constitute more that a "germ of an idea," and that the scope of the presently pending claims are clearly enabled by the specification. Therefore reconsideration and withdrawal of the rejection of claims 1-24 is respectfully requested.

Claims 20-23 were further rejected for lack of utility. The Office Action states that

> "the specification does not present any substantial or well-established utility for the claimed in vivo methods or compositions apart from use in methods of gene therapy...[a]t the time of filing, the relevant art considered gene therapy as a whole to be unpredictable as modes of delivery would and expression of genes encoding the therapeutic protein sufficient to provide alleviation of symptoms related to the target disease or condition had not been developed.

The Office Action cites a number of references in support of this position, including Blau *et al.* (1995), Crystal *et al.* (1995), Miller *et al.* (1995), Orkin *et al.* (1995), Verma *et al.* (1997), and Ross *et al.* (1996), and concludes,

> In view of the unpredictability and lack of success in the art at the time of filing, gene therapy can only be considered predictable in being shown not to work. Thus, to overcome these teachings in the art the specification would need to supply direct, correlative guidance as to the vector, the promoter, the expression level, the route of delivery and dosage amounts/frequency that are effective in alleviating symptoms of disease using the claimed expression system. Thus, the need for working examples in appropriate animal model studies is critical.

In response, Applicants submit that at the time the present application was filed, the future of gene therapy is often debated and there are numerous publications both in

support of gene therapy as a viable treatment as well those which cast doubt on the feasibility of gene therapy, such as those cited by the Examiner. A sample of published articles that discuss the state of gene therapy and that support the viability of gene therapy as a therapeutic approach is listed below (copies of which will be supplied upon request):

1) Anderson (1992) *Science*, 256: 808-813, which discusses clinical protocols regarding human gene therapy in an attempt to treat genetic and other diseases;

2) Friedmann (1989) *Science,* 244: 1275-1281, which discusses the scientific acceptance and feasibility of gene therapy for several disorders;

3) Miller (1992) *Nature*, 357: 455-460, which discusses the first human trials with gene therapy;

4) Crystal (1995) *Science*, 270: 404-410; which discusses the feasibility of gene transfer in humans; and

As evidence of the viability of gene therapy as a therapeutic approach, Applicants refer the Examiner's attention in particular to Crystal (1995) *Science*, 270, 404-410, in which the state of human gene therapy is reviewed. Contrary to the view presented in the Office Action, Crystal is optimistic about the success of gene therapy. Specifically, at page 405 the author concludes that:

> probably the most remarkable conclusion drawn from the human trials is that human gene transfer is indeed feasible. Although gene transfer has not been demonstrated in all recipients, most studies have shown that genes can be transferred to humans whether the strategy is *ex vivo* or *in vivo*, and that all vector types function as intended. Taken together, the evidence is overwhelming, with successful human gene transfer having been demonstrated in 28 ex vivo and 10 in vivo studies.

Miller et al., another reference relied upon to support instant rejection, also discloses that successful delivery of genes to specific sites and at high concentrations, has been achieved in patients suffering from ADA deficiency, HIV-infection or cancer (see page 197, second column, last paragraph). Moreover, Miller et al. teach that "the technology now exists to incorporate specific targeting features into most of the currently available delivery systems" (see page 190, second column, first paragraph) and that "it does not seem unrealistic ... that the gene therapy vectors of the future ... will be synthetic, custom designed vehicles into which specific targeting features can be included depending on the particular clinical requirements of the target disease and tissue" (see page 198, second column, first paragraph). Thus, Applicants respectfully submit that, based on the teachings of Miller et al., the ordinarily skilled artisan would reasonably expect that at the time of Applicants invention there existed technology which could be used to develop safe and highly efficient delivery systems.

Similarly, other references cited in the Office Action, Orkin and Verma, also acknowledge that some gene transfer does successfully take place, and that some benefit does exist for *in vivo* gene transfer. In addition, The United States Patent and Trademark Office has recognized the utility of gene therapy by issuing claims to gene therapy (see for example, U.S. Patent 5, 672,344).

Furthermore, by mid-1995 (the priority date of the instant application), a proliferation of gene therapy companies and of human gene therapy had occurred, indicating a general acceptance of the great importance of the field to medicine. For example, by the end of 1994, e.g. in a relatively short time from the founding of the industry, there were over 100 approved clinical protocols, and the number of patients

being treated by gene therapy techniques had doubled relative to 1993. See, for example, the editorial section of *The Lancet*, March 25, 1995, (vol. 345, pp. 739-940). The progress in clinical trials, the development of further gene therapy techniques, and the creation of numerous new gene therapy companies and gene therapy divisions of large pharmaceutical companies clearly demonstrates that methods and reagents were known in the art that have been successfully used for gene therapy.

Thus, it is Applicant's position that it would require no more than routine experimentation by one of ordinary skill in the art to determine appropriate regimens (e.g., amount, route of administration, time course of administration, etc.) for practicing the claimed *in vivo* methods. In *Cross v. Iizuka* (753 F.2d 1040 (Fed. Cir. 1985), the court established that the enablement requirements' how-to-use aspect is met when pharmacological activity in an *in vitro* environment is demonstrated and, accordingly, that the ordinarily skilled artisan can determine dosage levels for therapeutic administration without undue experimentation. While references exist which express doubts as to the efficacy of gene therapy, the fact remains that it has been used successfully. Furthermore, the fact that gene therapy trials for various therapeutic applications are ongoing, and, were approved at the time of filing of the instant application warrants that one of ordinary skill in the art finds credibility in this procedure. Accordingly, withdrawal of this rejection is respectfully requested.

Claim Rejections under 35 U.S.C. § 102

Claims 1, 4, 8, 13, 14, 16 and 20-24 were rejected as being anticipated by Deuschle *et al.* Claims 1, 5, 8, 14, 16, 20-24 were rejected as being anticipated by

Hannan *et al.* Claims 1-4, 9, 11, 13, 14, and 16-24 were rejected as being anticipated by Bujard *et al.* Applicants respectfully traverse these rejections.

None of the cited references teach first and second nucleic constructs in which the promoters are differentially regulated in tumor and non-tumor cells. Rather, the promoters used in the nucleic acid constructs taught by Deuschle *et al.*, Hannan *et al.*, and Bujard *et al.* are essentially constitutive promoters in which repression of the first gene is provided by the binding of the second gene product to the promoter of the first gene, and repression of the first gene is reversed by adding an *exogenous* substance (e.g., tetracycline) which interferes with the binding of the second gene product to the first promoter.

For example, Deuschle *et al.* teach a system in which the tetR-KRAB (second gene product) is constitutively expressed under the control of a CMV promoter (second promoter). A luciferase reporter gene (first gene) is under the control of another CMV promoter, which is associated with tetO sequences (CMV + tetO together forming the first promoter). The tetR domain of tetR-KRAB binds the tetO sequences from the first promoter and the KRAB domain prevents expression of the luciferase gene (first gene). Repression is lifted when tetracycline is added to the system, preventing tetR from binding to the tetO sequences in the first promoter. Hannan *et al.* and Bujard *et al.* merely teach similar systems using different constitutive promoters and exogenous substances.

Accordingly, reconsideration and withdrawal of these rejections is respectfully requested.

CONCLUSION

On the basis of the foregoing amendments and remarks, Applicants respectfully submit that the pending claims are in condition for allowance. If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is invited to call the undersigned at (617) 227-7400.

Date: August 15, 2001

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APPENDIX I

VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Amended) A composition ~~including~~ comprising a first nucleic acid construct ~~in which expression of~~ comprising a first gene whose expression is controlled by, a first promoter whose function is suppressed in non-tumor cells relative to tumor cells, and a second nucleic acid construct ~~in which expression of~~ comprising a second gene ~~for downregulating the~~ whose gene product suppresses expression of said first gene in non-tumor cells, wherein the expression of said second gene is controlled by a second promoter that is up-regulated in non-tumor cells relative to tumor cells, such that said first gene is expressed in tumor cells and suppressed in non-tumor cells.

2. (Amended) ~~A~~ The composition according to claim 1 wherein ~~expression of~~ said second gene ~~produces~~ of said second nucleic acid construct encodes an antisense RNA transcript complementary to a sequence within mRNA ~~produced on transcription of~~ encoded by said first gene of said first nucleic acid construct.

3. (Amended) ~~A~~ The composition according to claim 1 wherein ~~expression of~~ said second gene ~~produces~~ of said second nucleic acid construct encodes a ribozyme specific for a sequence within mRNA ~~produced on transcription of~~ encoded by said first gene of said first nucleic acid construct.

4. (Amended) ~~A~~ The composition according to claim 1 wherein ~~expression of~~ said second gene ~~produces~~ of said second nucleic acid construct encodes a sequence-specific transcriptional suppressor and said first nucleic acid construct ~~includes~~ comprises a

binding site ~~sequence for the~~ recognized by said sequence-specific transcriptional suppressor.

5. (Amended) ~~A~~ The composition according to claim 4 wherein said sequence-specific transcriptional suppressor is a *lac* operator suppressor.

6. (Amended) ~~A~~ The composition according to claim 4 wherein said sequence-specific transcriptional suppressor ~~includes~~ comprises a *tet* repressor DNA-binding domain and a transcriptional suppression domain of the *Drosphilia* KRAB transcription factor.

7. (Amended) ~~A~~ The composition according to claim 4 wherein said sequence-specific transcriptional suppressor ~~includes~~ comprises a Gal-4 DNA-binding domain and a transcriptional suppression domain of the *Drosphilia even-skipped* transcription factor.

8. (Twice Amended) ~~A~~ The composition according to claim 1 wherein said first nucleic acid construct and said second nucleic acid construct are each on separate nucleic acid vectors.

9. (Twice Amended) ~~A~~ The composition according to claim 1 wherein said first nucleic acid construct and said second nucleic acid construct are on ~~the same~~ a single nucleic acid vector.

10. (Amended) ~~A~~ The composition according to claim 9 ~~including~~ comprising an insulator sequence between said first nucleic acid construct and said second nucleic acid construct.

11. (Twice Amended) ~~A~~ The composition according to claim 10 wherein ~~a~~ said nucleic acid vector is a viral vector.

12. (Twice Amended) ~~A~~ The composition according to claim 1 wherein said second promoter of said second nucleic acid construct ~~includes~~ comprises a p53 binding site sequence or ~~CMB~~ CMV promoter.

13. (Amended) ~~A~~ The composition according to claim 12 wherein said second nucleic acid construct ~~includes~~ comprises said p53 binding site sequence downstream of a TATA Box and downstream of the transcriptional start site of said second promoter of said second nucleic acid construct.

14. (Twice Amended) ~~A~~ The composition according to claim 1 wherein said first promoter of said first nucleic acid construct is up-regulated in tumor cells relative to non-tumor cells.

15. (Amended) ~~A~~ The composition according to claim 14 wherein said first promoter is the HSP70 promoter.

16. (Twice Amended) ~~A~~ The composition according to claim 1 wherein said first gene is a reporter gene.

17. (Twice Amended) ~~A~~ The composition according to claim 1 wherein said first gene encodes an antitumour agent.

18. (Amended) ~~A~~ The composition according to claim 17 wherein said antitumour agent is a pro-drug activating enzyme.

19. (Amended) ~~A~~ The composition according to claim 18 wherein said pro-drug activating enzyme is a thymidine kinase.

21. (Amended) ~~A~~ The cell according to claim 20 which is a tumor cell.

23. (Amended) ~~A~~ The method according to claim 22 wherein said cell is a tumor cell.

24. (Twice Amended) ~~A~~ The method according to claim 23 wherein said first nucleic acid construct and said second nucleic acid construct are introduced into said cell *in vitro*.

APPENDIX II

Pending Claims

1. (Amended) A composition comprising a first nucleic acid construct comprising a first gene whose expression is controlled by a first promoter whose function is suppressed in non-tumor cells relative to tumor cells, and a second nucleic acid construct comprising a second gene whose gene product suppresses expression of said first gene, wherein the expression of said second gene is controlled by a second promoter that is up-regulated in non-tumor cells relative to tumor cells, such that said first gene is expressed in tumor cells and suppressed in non-tumor cells.

2. (Amended) The composition according to claim 1 wherein said second gene of said second nucleic acid construct encodes an antisense RNA transcript complementary to a sequence within mRNA encoded by said first gene of said first nucleic acid construct.

3. (Amended) The composition according to claim 1 wherein said second gene of said second nucleic acid construct encodes a ribozyme specific for a sequence within mRNA encoded by said first gene of said first nucleic acid construct.

4. (Amended) The composition according to claim 1 wherein said second gene of said second nucleic acid construct encodes a sequence-specific transcriptional suppressor and said first nucleic acid construct comprises a binding site recognized by said sequence-specific transcriptional suppressor.

5. (Amended) The composition according to claim 4 wherein said sequence-specific transcriptional suppressor is a *lac* operator suppressor.

6. (Amended) The composition according to claim 4 wherein said sequence-specific transcriptional suppressor comprises a *tet* repressor DNA-binding domain and a transcriptional suppression domain of the *Drosphilia* KRAB transcription factor.

7. (Amended) The composition according to claim 4 wherein said sequence-specific transcriptional suppressor comprises a Gal-4 DNA-binding domain and a transcriptional suppression domain of the *Drosphilia even-skipped* transcription factor.

8. (Twice Amended) The composition according to claim 1 wherein said first nucleic acid construct and said second nucleic acid construct are each on separate nucleic acid vectors.

9. (Twice Amended) The composition according to claim 1 wherein said first nucleic acid construct and said second nucleic acid construct are on a single nucleic acid vector.

10. (Amended) The composition according to claim 9 comprising an insulator sequence between said first nucleic acid construct and said second nucleic acid construct.

11. (Twice Amended) The composition according to claim 10 wherein said nucleic acid vector is a viral vector.

12. (Twice Amended) The composition according to claim 1 wherein said second promoter of said second nucleic acid construct comprises a p53 binding site sequence or CMV promoter.

13. (Amended) The composition according to claim 12 wherein said second nucleic acid construct comprises said p53 binding site sequence downstream of a TATA Box and downstream of the transcriptional start site of said second promoter of said second nucleic acid construct.

14. (Twice Amended) The composition according to claim 1 wherein said first promoter of said first nucleic acid construct is up-regulated in tumor cells relative to non-tumor cells.

15. (Amended) The composition according to claim 14 wherein said first promoter is the HSP70 promoter.

16. (Twice Amended) The composition according to claim 1 wherein said first gene is a reporter gene.

17. (Twice Amended) The composition according to claim 1 wherein said first gene encodes an antitumour agent.

18. (Amended) The composition according to claim 17 wherein said antitumour agent is a pro-drug activating enzyme.

19. (Amended) The composition according to claim 18 wherein said pro-drug activating enzyme is a thymidine kinase.

20. (Amended) A cell containing a first nucleic acid construct and a second nucleic acid construct of a composition according to claim 1.

21. (Amended) The cell according to claim 20 which is a tumor cell.

22. (Amended) A method comprising introduction of a first nucleic acid construct and a second nucleic acid construct of a composition according to claim 1 into a cell.

23. (Amended) The method according to claim 22 wherein said cell is a tumor cell.

24. (Twice Amended) The method according to claim 23 wherein said first nucleic acid construct and said second nucleic acid construct are introduced into said cell *in vitro*.